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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/786,998
Filing Date: June 14, 2001
Appellant(s): PACCIARINI ET AL.

Peter I. Bernstein
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed February 06, 2007 appealing from the Office action mailed December 20, 2006.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

5,304,687	Bargiotti et al	4-1994

Kuhl, J.S. et al "Effects of the methoxymorpholino derivative of doxorubicin and its bioactivated form versus doxorubicin on human leukemia and lymphoma cell lines and normal bone marrow", Cancer Chemother Pharmacol. Vol. 33, (1993), pp. 10-16.

Nakamura, H. et al "Large-Dose intra-arterial injection of lipidol in liver cancer" Gan To Kagaku Ryoho 8 Pt 2 (1988), pp. 2562-7, English Abstract.

Gorbunova, V.A. "Intrahepatic Arterial Infusion Chemotherapy for Primary and Metastatic Cancer of the Liver, 1990.

(9) Grounds of Rejection

The following ground(s) of rejection as advanced in office actions of record are applicable to the appealed claims:

Claims 13-14 and 18-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bargiotti et al (US 5,304,687) in combination with Kuhl et al (Cancer Chemother. Pharmacol., 1993, 33, 10-16), Nakamura et al (Gan. To Kagaku Ryoho 1988, Aug. 15 (8 Pt 2), 2562-7, English Abstract) and Gorbunova (Intrahepatic Arterial Infusion Chemotherapy for Primary and Metastatic Cancer of the Liver, 1990).

Bargiotti et al, drawn to morpholino derivatives of anthracyclines teach methoxy morpholino doxorubicin (col. 1, lines 10-62; compounds A4 and A5). These derivatives are shown to inhibit solid tumors such as human carcinoma with intravenous and oral route (col. 11, lines 62-68; col. 12, Table 6). However, the intrahepatic route of administration is not specifically taught.

Kuhl, drawn to doxorubicin derivatives, teaches that the methoxymorpholino derivative of doxorubicin has a broad-spectrum antitumor activity and is non-cross-resistant in multi drug

tumor resistant models. It is also activated in the liver to a metabolite which crosslinks to DNA and is 10 times more potent (Abstract, page 10).

Nakamura et al teach that intra-arterial infusion of lipiodol (iodized oil) and adriamycin (same as doxorubicin) showed remarkable therapeutic effects for advanced cancer (English abstract).

Gorbunova teaches in general that intra hepatic arterial infusion chemotherapy allows for creating a super high concentration of an antitumor agent in the organ affected by the tumor (English abstract).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a composition comprising methoxymorpholino doxorubicin with iodized oil and use the same in a method of treating a human liver tumor and reducing systemic exposure as instantly claimed since such is seen to be taught in the prior art. It is well within the purview of one of ordinary skill in the art to adjust dosages and the frequency of administration based on that taught in the prior art.

One of ordinary skill in the art would have been motivated to use MMDX (methoxymorpholino doxorubicin) in hepatic artery administration since prior art recognizes that hepatic artery administration of doxorubicin is beneficial in treating tumor and reducing systemic exposure. Hepatic arterial administration also creates super high concentrations in the organ affected. This localized administration is beneficial for reducing systemic exposure and reducing tumor volume in the liver. It is logical that lipiodol (iodized oil) be administered in combination with MMDX since it has shown therapeutic effects when administered with the closely related

adriamycin (adriamycin is the Trade name for doxorubicin and structurally very close to MMDX).

(10) Response to Argument

Applicants argue that a claims 13 and 14 are patentable over the prior art of record because:

Bargiotti et al the principal reference teaches the utility of morpholino derivatives of anthracyclines of which MMDX to be antitumor activity in murine animals and is administered by intravenous or oral route. It does not teach or suggest pharmaceutical compositions which includes MMDX or an acceptable salt or its administration into the hepatic artery.

Kuhl discloses that MMDX is activated in the liver to produce a metabolite having high potency. There is no disclosure of MMDX composition which remains selectively in the liver after injection.

Nakamura is directed to a disclosure of clinical trials of intarhepatically administered iodized oil and doxorubicin hydrochloride in treatment of liver tumors. The instant claims are directed to an entirely distinguished compound from doxorubicin (DOX). In view of the selectivity of compounds in the treatment of cancer and the chemically distinguished nature of the compounds DOX and MMDX the failure of Nakamura to suggest MMDX is evidence of patentable distinction.

Gorbunova discloses only administration and dosage of DOX in intrahepatic treatment of liver tumors. Gorbunova teaches a chemically distinct compound.

The instant claims are drawn to pharmaceutical compositions comprising an active principle MMDX and pharmaceutically acceptable agent which remains selectively I the liver tumor after injection through hepatic artery and wherein the agent is iodized oil.

According to Bagriotti et al MMDX has shown to inhibit solid tumors (col. 11, lines 65-68) and according to Kuhl it is activated in the liver to a highly active metabolite. Iodized oil in combination with adriamycin (same as doxorubicin) via intra-arterial infusion shows remarkable therapeutic effect. Hence one of skill in the art would be motivated to make the compositions as instantly claimed since MMDX is structurally very close to doxorubicin and is known to be used in treatment of tumors. They are not entirely distinguished compounds as applicants claim. Similarity in structure and function of the active agent entails motivation for making the composition as instantly claimed.

Applicants argue that claims 18, 20-23, 26 and 27 are patentable over the prior art because:

Bargiotti et al the principal reference teaches the utility of morpholino derivatives of anthracyclines of which MMDX to be antitumor activity in murine animals.

Kuhl teaches effectiveness of MMDX in certain blood tumors and there is no expectation of success for using MMDX in treatment of liver tumors.

Nakamura teaches intrahepatic administration of doxorubicin (DOX) in the treatment of liver tumors. But the compound of the instant claims, MMDX is chemically and structurally different. Gorbunov's teaching is substantially the same as Nakamura.

According to Bargiotti et al MMDX is an agent known to inhibit solid tumors (col. 11, lines 65-68) and according to Kuhl it (MMDX) is activated in the liver to a highly active metabolite. Kuhl may not teach the use of MMDX for solid tumors. But Bargiotti teaches that MMDX is known to inhibit tumor. One of skill in the art will recognize from the teaching of Kuhl that since MMDX is know to inhibit solid tumors (according to Bargiotti) and it is also metabolized to the highly active metabolite in the liver it is logical to use MMDX for treatment of liver tumor. According to Gorbunova intra-arterial infusion chemotherapy allows for the creation of super high concentrations of the antitumor agent in the organ affected by the tumor. One of skill in the art will recognize from this teaching of Gorbunova that intrarterial infusion of MMDX (which is also metabolized to an active metabolite in the liver) will accumulate in the liver if liver is affected by tumor. Since Iodized oil in combination with adriamycin (same as doxorubicin and structurally very close to MMDX) via intra-arterial infusion shows remarkable therapeutic effect, one of skill in the art would be motivated to make the compositions of MMDX with iodized oil as instantly claimed and use it in a method treatment of tumors. There is a reasonable expectation of success from the teachings of the prior art. MMDX and DOX are not entirely distinguished compounds as applicants claim. Similarity in structure and function of the active agent entails motivation for making the compounds and their compositions as instantly claimed.

Applicants argue that claims 24-25 and 28-30 are patentable over the prior art of record because:

Claims 24-25 are drawn to frequency of administration of the active agent and claims 28-30 are drawn to the dosage of the active agent. The showings presented in the instant

specification show the effectiveness of the method of treatment of liver cancer but also concentrations consistent with reduced systemic exposure to MMDX.

Since intra-arterial administration creates a high concentration in the organ affected by the tumor, one of skill in the art would expect reduced systemic exposure of the active agent since the active agent can be directly administered to the liver (where the tumor or cancer is present) via intrahepatic arterial infusion. Since such an infusion also creates high concentration of the active agent in the liver (the organ affected by the tumor) toxicity will be only with respect to the tumor cells in the liver. Systemic toxicity is reduced. One of skill in the art will recognize this fact form the teachings of the prior art.

Applicants argue that claim 31 is patentable over the prior art because:

The prior art does not teach the intrahepatic administration of therapeutically effective amount of a composition comprising MMDX and the requirement that the MMDX pharmaceutical composition remains selectively in the liver tumor after its injection through the hepatic artery is not disclosed in the applied references. The requirement that MMDX be administered by injection through the hepatic artery is also not taught in any of the references.

According to Gorbunova intrahepatic arterial infusion chemotherapy allows for the creation of super high concentrations of the antitumor agent in the organ affected by the tumor. One of skill in the art will recognize from this teaching of Gorbunova that intrahepatic arterial infusion of MMDX (which is also metabolized to an active metabolite in the liver) will

accumulate in the liver if liver is affected by tumor. According to Bargiotti et al MMDX is an agent known to inhibit solid tumors.

The Examiner has presented arguments above addressing arguments of the applicants.

For the reasons discussed above, it is believed that the rejections should be sustained.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

G. Krishnan

Ganapathy Krishnan
Patent Examiner, AU 1623
June 04, 2007

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